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- [54] **S-ALKYL-ISOTHIOUREIDO-AMINO ACIDS AND USE THEREOF**
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- [58] Field of Search **558/5; 514/508**

[56] **References Cited****U.S. PATENT DOCUMENTS**

- 5,216,025 6/1993 Gross et al. 514/565
- 5,281,627 1/1994 Griffith 514/565
- 5,296,466 3/1994 Kilbourn et al. 514/6

FOREIGN PATENT DOCUMENTS

- 1096894 1/1961 Germany .
- 1804894 8/1969 Germany .

OTHER PUBLICATIONS

- Adnot, S., et al, Chem. Abstr. 119:46606f (1992).
- Hishikawa, K., Chem. Abstr. 117:5022c (1992).
- Griffith, O. W., et al, poster titled "Inhibitions of Nitric Oxide Synthase: Structural Constraints on Binding and Mechanism of Action" presented at the 3rd International Meeting on the Biology of Nitric Oxide, Cologne, Germany, Oct. 1993.
- Bodanszky, M., et al, The Practice of Peptide Synthesis, Springer-Verlag, New York, 1984, pp. 48, 49, 153, 154.
- Feldman, P. L., Tetrahedron Lett., 32, 875-878, 1991.
- Rees, D. D., et al, Br. J. Pharmacol., 96, 418-424 (1989).

Gray, G. A., et al, Br. J. Pharmacol., 103, 1218-1224 (May 1991).

Aisaka, K., et al, Biochem. Biophys. Res. Commun. 163, No. 2, 710-717 (Sep. 15, 1989).

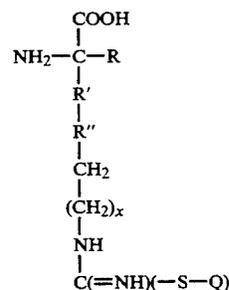
Jolou-Schaeffer, G., et al, Am. J. Physiol. 259, H1038-H1043, Oct. 1990.

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[57] **ABSTRACT**

Inhibitors of nitric oxide formation from arginine useful for treating hypotension, inflammation, stroke and to restore vascular contractile sensitivity to the effects of α_1 -adrenergic agonists are physiologically active compounds including N δ -substituted ornithine or N ϵ -substituted lysine moieties or monoalkyl carbon-substituted N δ -substituted ornithine or N ϵ -substituted lysine moieties, having the formula



wherein R is (CH₂)_yCH₃ or H, R' is CH₂ or C(H)(CH₂)_yCH₃, and R'' is CH₂ or C(H)(CH₂)_yCH₃, with y ranging from 0 to 5, and x is 0 or 1 and wherein none or only one of R, R' and R'' provides an alkyl substituent on ornithine or lysine moiety, and wherein Q is alkyl having 1 to 5 carbon atoms, and physiologically acceptable acid addition salts thereof.

17 Claims, 5 Drawing Sheets